Medicines & Healthcare products Regulatory Agency

MHRA

Public Assessment Report

National Procedure

HEPLISAV B 20 micrograms solution for injection in pre-filled syringe
Hepatitis B vaccine (recombinant DNA, adjuvanted)

(Hepatitis B surface antigen (HBsAg)[1,2])

PLGB 55725/0001

Dynavax GmbH

[1] Adjuvanted with 3000 micrograms CpG 1018 adjuvant, a 22-mer immunostimulatory sequence oligonucleotide
[2] Produced in yeasts cells (*Hansenula polymorpha*) by recombinant technology

LAY SUMMARY
HEPLISAV B 20 micrograms solution for injection in pre-filled syringe
Hepatitis B vaccine (recombinant DNA, adjuvanted)

(Hepatitis B surface antigen (HBsAg) [1,2])

This is a summary of the Public Assessment Report (PAR) for HEPLISAV B 20 micrograms solution for injection in pre-filled syringe, Hepatitis B vaccine (recombinant DNA, adjuvanted). It explains how this product was assessed and its authorisation recommended, as well as its conditions of use. It is not intended to provide practical advice on how to use this product.

This product will be referred to as HEPLISAV B in this lay summary for ease of reading.

This product has been authorised by MHRA for Great Britain (consisting of England, Scotland and Wales). In coming to its decision, MHRA has relied on a European Commission (EC) decision on 18 February 2021 (EMEA/H/C/005063), in accordance with the advice from the Committee for Medicinal Products for Human Use (CHMP). This is known as the EC Decision Reliance Procedure.

This application was approved under Regulation 50 of the Human Medicines Regulation 2012, as amended (previously Article 8.3 of Directive 2001/83/EC, as amended).

For practical information about using for HEPLISAV B, patients should read the Patient Information Leaflet (PIL) or contact their doctor or pharmacist.

What is HEPLISAV B and what is it used for?
HEPLISAV B is a vaccine for use in adults 18 years of age and older to protect against infection with the hepatitis B virus.

HEPLISAV B may also protect against hepatitis D which can only occur in people who have hepatitis B infection.

What is Hepatitis B?
- Hepatitis B is an infectious illness of the liver, caused by a virus. Hepatitis B virus infection can cause serious liver problems such as “cirrhosis” (scarring in the liver) or liver cancer.

- Some people infected with the hepatitis B virus become carriers, which means that they may not feel ill but continue to have the virus in their body and they can still infect other people.

- The disease spreads by the hepatitis B virus entering the body through contact with an infected person’s body fluids, such as in the vagina, blood, semen, or spit (saliva). A mother who is a carrier of the virus can also pass the virus to her baby at birth.

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- The main signs of the illness include mild signs of flu (such as headache and fever, feeling very tired, dark urine, pale stools (faeces), yellowing of the skin and eyes (jaundice)). However, some people with hepatitis B do not look or feel ill.

How does HEPLISAV B work?
When a person is given the HEPLISAV B vaccine, it helps the body's natural defence system (immune system) produce specific protection (antibodies) against the hepatitis B virus.

- HEPLISAV B contains an adjuvant, a substance which improves the body's production of antibodies and makes the protection last for longer.
- A course of two injections of HEPLISAV B is required to provide full protection against hepatitis B.
- HEPLISAV B is not used to treat a person who is already infected with the hepatitis B virus, including people infected with the hepatitis B virus and have become carriers for infection.

How is HEPLISAV B used?
The pharmaceutical form of this medicine is a solution for injection in pre-filled syringe and the route of administration is as an injection into the muscle, usually in the upper arm, given by a doctor, pharmacist or nurse.

For adults, the course of vaccination is two injections:
- the first injection on a date agreed upon with your doctor or nurse.
- the second injection 1 month after the first injection.

If the patient forgets a return visit to receive HEPLISAV B, they should talk to their doctor and arrange another visit.

The patient should make sure they complete the injections, or they may not be fully protected. Once the patient has had the first injection of HEPLISAV B, the second injection must also be HEPLISAV B (not another type of hepatitis B vaccine).

For further information on how HEPLISAV B is used, refer to the PIL and Summary of Product Characteristics (SmPC) available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

This medicine can only be obtained with a prescription.

The patient should ask the administering healthcare practitioner if they have any questions concerning their medicine.

What benefits of HEPLISAV B have been shown in studies?
Results from three main studies involving over 13,000 participants showed that HEPLISAV B was more effective than Engerix B (another hepatitis B vaccine) at stimulating an immune response against the virus. Taken together the studies found that around 96% of people given HEPLISAV B developed enough antibodies to kill off the virus and protect against the disease compared with 80% of those given Engerix B.

People given HEPLISAV B also had higher levels of antibodies and sufficient levels developed earlier with HEPLISAV B than with Engerix B.

What are the possible side effects of HEPLISAV B?
The most common side effects with HEPLISAV B (which may affect more than 1 in 10 people) are headache, muscle aches, feeling tired, pain at the spot where the injection was given and feeling unwell (malaise).

For the full list of all side effects reported with this medicine, see Section 4 of the PIL or the SmPC available on the MHRA website.

If a patient gets any side effects, they should talk to their doctor, pharmacist or nurse. This includes any possible side effects not listed in the product information or the PIL that comes with the medicine. Patients can also report suspected side effects themselves, or a report can be made on their behalf by someone else who cares for them, directly via the Yellow Card scheme at https://yellowcard.mhra.gov.uk or search for 'MHRA Yellow Card' online. By reporting side effects, patients can help provide more information on the safety of this medicine.

Why was HEPLISAV B approved?
Studies have shown that HEPLISAV B provides protection against hepatis B infection in 96% of people given the vaccine. Side effects occurred slightly less frequently with this vaccine than with the comparator vaccine (Engerix B) and they are considered manageable.

The MHRA therefore concluded that HEPLISAV B's benefits are greater than its risks and it can be authorised for use in Great Britain.

What measures are being taken to ensure the safe and effective use of HEPLISAV B?
As for all newly authorised medicines, a Risk Management Plan (RMP) has been developed for HEPLISAV B. The RMP details the important risks of HEPLISAV B, how these risks can be minimised, any uncertainties about HEPLISAV B (missing information), and how more information will be obtained about the important risks and uncertainties.

The following safety concerns have been recognised for HEPLISAV B:

Summary of Safety Concerns	
Important Identified Risks	None
Important Potential Risks	Exacerbation of potentially immune-mediated disorders (including inflammatory disorders) in individuals with a history of immune-mediated disorder
Missing Information	Safety in pregnancy and lactation Safety in immunocompromised patients including persons living with HIV Concomitant administration with other vaccines

The information included in the SmPC and the PIL is compiled based on the available quality, non-clinical and clinical data, and includes appropriate precautions to be followed by healthcare professionals and patients. Side effects of HEPLISAV B are continuously

monitored and reviewed including all reports of suspected side-effects from patients, their carers, and healthcare professionals.

In addition to the safety information provided in the HEPLISAV B product information, the Marketing Authorisation Holder (MAH) has committed to additional pharmacovigilance activities through the provision of safety data derived from a pregnancy registry.

An RMP and a summary of the pharmacovigilance system have been provided with this application and are satisfactory.

Other information about HEPLISAV B
A marketing authorisation was granted in Great Britain on 24 February 2023.

The full PAR for HEPLISAV B follows this summary.

This summary was last updated in February 2024.

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I. INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Medicines and Healthcare products Regulatory Agency (MHRA) considered that the application for HEPLISAV B 20 micrograms solution for injection in pre-filled syringe, Hepatitis B vaccine (recombinant DNA, adjuvanted) (PLGB 55725/0001) could be approved.

The product is approved for the following indications:

- HEPLISAV B is indicated for active immunisation against hepatitis B virus infection (HBV) caused by all known subtypes of hepatitis B virus in adults 18 years of age and older.

  The use of HEPLISAV B should be in accordance with official recommendations.

  It can be expected that hepatitis D will also be prevented by immunisation with HEPLISAV B as hepatitis D (caused by the delta agent) does not occur in the absence of hepatitis B infection.

HEPLISAV B is comprised of recombinant hepatitis B surface antigen and the CpG 1018 adjuvant, which is a 22-mer immunostimulatory sequence oligonucleotide.

HEPLISAV B induces specific antibodies against HBsAg (anti-HBs).

The biological actions of CpG 1018 are exerted locally at the injection site and draining lymph nodes. The adjuvant CpG 1018 component of HEPLISAV B has the following effects: (1) activates plasmacytoid dendritic cells (pDCs) through the pattern recognition receptor Toll-like receptor 9; (2) converts pDCs into highly efficient antigen-presenting cells that present the processed HBsAg to CD4+ T cells; and, (3) promotes Th1 T-cell differentiation through the production of IFN-alpha and IL-12. This activation results in a high and sustained antibody response, likely due to the rapid generation of large numbers of anti-HBs-secreting plasmacytes and HBsAg-specific memory B and T cells.

This product has been authorised by MHRA for Great Britain (consisting of England, Scotland and Wales). In coming to its decision, MHRA has relied on a European Commission (EC) decision on 18 February 2021 (EMEA/H/C/005063), in accordance with the advice from the Committee for Medicinal Products for Human Use (CHMP).

For the scientific discussion of the quality, non-clinical and clinical assessment conducted by the European Medicines Agency (EMA), please refer to the European Public Assessment Report, available on the EMA website.

This application was approved under Regulation 50 of the Human Medicines Regulation 2012, as amended (previously Article 8.3 of Directive 2001/83/EC, as amended).

In line with the legal requirements for children's medicines, the application included a licensing authority decision on the agreement of a paediatric investigation plan (PIP) (MHRA-100557-PIP01-22-M01) which includes a waiver for development in paediatrics for all age subsets.

The MHRA has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for this product at all sites responsible for the manufacture, assembly and batch release of this product.

A Risk Management Plan (RMP) and a summary of the pharmacovigilance system have been provided with this application and are satisfactory.

A marketing authorisation was granted on 24 February 2023.

II. PRODUCT INFORMATION

SUMMARY OF PRODUCT CHARACTERISTICS (SmPC)

The SmPC is in line with current guidelines and was satisfactory.

PATIENT INFORMATION LEAFLET (PIL)

The PIL is in line with current guidelines and is satisfactory.

LABEL

The labelling is in line with current guidelines and is satisfactory.

III. QUALITY ASPECTS

The MHRA considered that the quality data submitted for this application is satisfactory.

The grant of a marketing authorisation was recommended.

IV. NON-CLINICAL ASPECTS

The MHRA considered that the non-clinical data submitted for this application is satisfactory.

The grant of a marketing authorisation was recommended.

V. CLINICAL ASPECTS

The MHRA considered that the clinical data submitted for this application is satisfactory.

The grant of a marketing authorisation was recommended.

VI. RISK MANAGEMENT PLAN (RMP)

The applicant has submitted an RMP, in accordance with the requirements of Regulation 182 of The Human Medicines Regulation 2012, as amended. In addition to routine pharmacovigilance and risk minimisation measures, the following additional pharmacovigilance measures have been proposed:

Table 1. Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Exacerbation of potentially immune-mediated disorders (including inflammatory disorders) in individuals with a history of immune-mediated disorder	No risk minimisation measures planned	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Safety in pregnancy and lactation	Routine Risk Minimisation Measures: Section 4.6 of the SmPC PL Section 2 regarding lack of data Subject to medical prescription Additional Risk Minimisation Measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: HBV-27: Pregnancy Registry
Safety in immunocompromised patients including persons living with HIV	Routine Risk Minimisation Measures: Section 4.4 of the SmPC Refer to PL Section 2 Subject to medical prescription Additional Risk Minimisation Measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Concomitant administration with other vaccines	Routine Risk Minimisation Measures:	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:
	See Section 4.5 of the SmPC Subject to medical prescription Additional Risk Minimisation Measures: None	None Additional pharmacovigilance activities: None

This is acceptable.

VII. USER CONSULTATION

A text draft of the Patient Information Leaflet (PIL) was presented. A commitment to provide a mock-up and evidence of user consultation of the PIL to the MHRA prior to marketing was accepted.

VIII. OVERALL CONCLUSION, BENEFIT/RISK AND RECOMMENDATION

The quality of the product is acceptable. The non-clinical and clinical data submitted have shown the positive benefit/risk of this product in the active immunisation against hepatitis B virus infection (HBV) caused by all known subtypes of hepatitis B virus in adults 18 years of age and older. It can be expected that hepatitis D will also be prevented by immunisation with HEPLISAV B as hepatitis D (caused by the delta agent) does not occur in the absence of hepatitis B infection.

The SmPC, PIL and labelling are satisfactory.

In accordance with legal requirements, the current approved GB versions of the SmPC and PIL for this product are available on the MHRA website.

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Steps taken after the initial procedure with an influence on the Public Assessment Report (non-safety variations of clinical significance).

Please note that only non-safety variations of clinical significance are recorded below and in the annexes to this PAR. The assessment of safety variations, where significant changes are made, is recorded on the MHRA website or European Medicines Agency (EMA) website. Minor changes to the marketing authorisation are recorded in the current SmPC and/or PIL available on the MHRA website.

Application type	**Scope**	**Product information affected**	**Date of grant**	**Outcome**	**Assessment report attached Y/N**